Chrysin

Pharmacy Compounding Advisory Committee Meeting

June 23, 2016

Michael Brave, MD

Clinical Reviewer

Division of Oncology Products 1 (DOP1)

Office of Hematology and Oncology Products (OHOP)

Chrysin Review Team

Michael Brave, MD, Clinical Reviewer, DOP1/OHOP

Haw-Jyh Chiu, PhD, Pharmacology/Toxicology Reviewer, DHOT/OHOP

Ben Zhang, PhD, Chemistry Reviewer, Office of Pharmaceutical Quality (OPQ)

V. Ellen Maher, MD, Clinical Team Leader, DOP1/OHOP

Geoffrey Kim, MD, Division Director, DOP1, OHOP

Todd Palmby, PhD, Supervisory Pharmacologist/Toxicologist, DHOT/OHOP

Ramesh Sood, PhD, Senior Scientific Director (Acting), OPQ

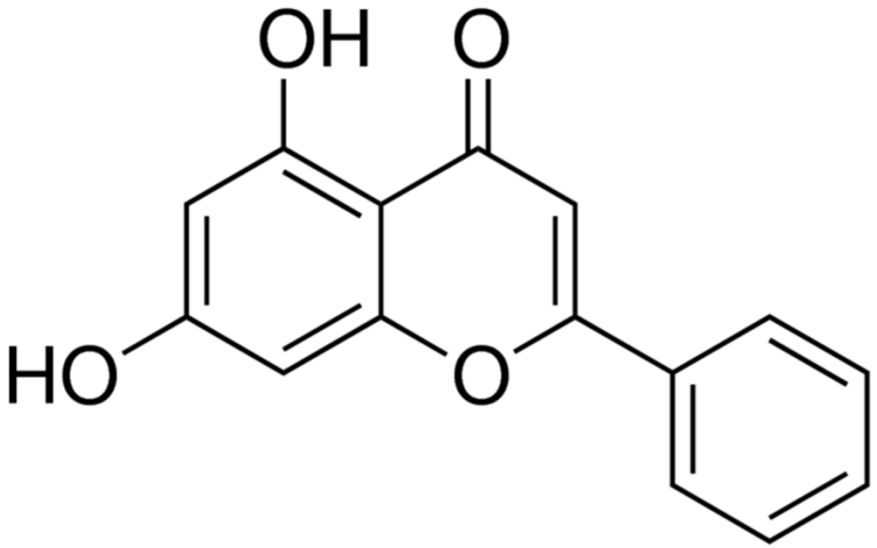
Christine Nguyen, MD, Deputy Director for Safety, Division of Bone, Reproductive and Urologic Products (DBRUP), Office of Drug Evaluation III (ODE III)

Audrey Gassman, MD, Deputy Director, DBRUP, ODE III

Chrysin: Background

- Nomination
  - Use: “As an aromatase inhibitor which prevents the conversion of testosterone to estrogen” for the treatment of “high estrogen and low testosterone.”
  - Route of administration: Topical
  - References provided in the nomination do not include clinical safety or efficacy data for chrysin, although they do include nonclinical information.
- Currently available as a dietary ingredient in dietary supplements

What is Chrysin?



Chemistry Considerations for Chrysin

- Extracted from plant material or bee propolis
- Small molecule that can be easily characterized
- Stable under ordinary storage conditions for topical dosage forms

Non-Clinical Data: Potential Mechanisms of Action

- Lethal dose to 50% of cells (LD_{50}) in micromolar range against various cancer cell lines
- Xenograft studies suggest pleotropic mechanisms of action
  - Carcinogen biotransformation
  - Free radical scavenging
  - Modulates cellular pathways linked to inflammation, proliferation, differentiation and metastasis

Bioavailability

- Poor oral absorption
- No available information on systemic exposure from topical application

Disposition and metabolism of the flavonoid chrysin in normal volunteers

T. Walle, Y. Otake, J. A. Brubaker, U. K. Walle & P. V. Halushka

Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Division of Clinical Pharmacology, Medical University of South Carolina, Charleston, SC 29425, USA

Aims To describe the oral disposition of the dietary flavonoid chrysin in healthy volunteers.
Methods Oral 400 mg doses of chrysin were administered to seven subjects. Chrysin and metabolites were assayed in plasma, urine and faeces by h.p.l.c.
Results Peak plasma chrysin concentrations were only 3–16 ng ml^{-1} with AUCs of 5–193 ng ml^{-1} h. Plasma chrysin sulphate concentrations were 30-fold higher (AUC 450–4220 ng ml^{-1} h). In urine, chrysin and chrysin glucuronide accounted for 0.2–3.1 mg and 2–26 mg, respectively. Most of the dose appeared in faeces as chrysin. Parallel experiments in rats showed high bile concentrations of chrysin conjugates.
Conclusions These findings, together with previous data using Caco-2 cells, suggest that chrysin has low oral bioavailability, mainly due to extensive metabolism and efflux of metabolites back into the intestine for hydrolysis and faecal elimination.

Evaluation of Effectiveness

- No effect of oral chrysin on testosterone levels

JOURNAL OF MEDICINAL FOOD
J Med Food 6 (4) 2003, 387–390

Effects of Chrysin on Urinary Testosterone Levels in Human Males

Cristiana Gambelunghe,[1] Ruggero Rossi,[1] Marco Sommavilla,[1] Chiara Ferranti,[1] Riccardo Ross
Chiara Ciculi,[2] Stefania Gizzi,[2] Alessandra Micheletti,[2] and Stefano Rufini[2]

[1]Department of Clinical and Experimental Medicine, Division of Sports Medicine-Laboratorio delle Attività Motorie e Sportive; and [2]Department of Clinical and Experimental Medicine, Division of Pharmacology, University of Perugia, Perugia, Italy

ABSTRACT The equilibrium of sexual hormones in both sexes is controlled in vertebrates by the enzyme aromatase, a member of the cytochrome P450 superfamily, which catalyzes the conversion of androstenedione and testosterone into estrone and estradiol, respectively. Flavonoids are diphenolic compounds present in whole grains, legumes, fruits, and vegetables that are strongly implicated as protective in coronary heart disease, stroke, and cancer. One flavonoid, chrysin, found in high concentrations in honey and propolis, has been shown to be an inhibitor of aromatase enzyme activity. These foods are often used as supplements, particulary by sportsmen for their energetic and antioxidant properties. The aim of this study was to verify if daily treatment for 21 days with propolis and honey, containing chrysin, would modify urinary concentrations of testosterone in volunteer male subjects. In fact, aromatase inhibition by chrysin could block the conversion of androgens into estrogens with a consequent increase of testosterone, eventually measurable in urine samples. The obtained data did not show alterations of the levels of testosterone in the volunteers after 7, 14, and 21 days of treatment in comparison with baseline values and compared with measurements on the control subjects at the same time. In conclusion, the use of these foods for 21 days at the doses usually taken as oral supplementation does not have effects on the equilibrium of testosterone in human males.

Evaluation of Effectiveness

- Biological (nonclinical) effects may support rationale for development as a chemopreventive agent or as adjunct to chemotherapy
- No clinical anticancer or hormone modifying activity demonstrated with oral or topical formulations
- FDA-approved aromatase inhibitors for the treatment of cancer are available
- FDA-approved testosterone replacement products are available

Evaluation of Safety

- Nonclinical
  - Cytotoxic at high doses (Rainbow trout hepatocytes)
  - Positive bacterial mutagen assay (Salmonella TA100)
  - No developmental or reproductive toxicology data
  - No carcinogenicity data

- Clinical
  - No toxicity attributable to chrysin in clinical trials or adverse event reporting

Historical Use in Compounding

- Insufficient information found to determine how long chrysin has been used in pharmacy compounding
- Currently, availability of oral and topical compounded formulations are advertised on the internet

Summary

- Well-characterized substance stable in topical formulations
- No clinical anticancer or hormone modifying activity demonstrated with oral or topical formulations
- Clinical safety issues have not been identified; nonclinical data suggest potential concerns
- FDA-approved products available for hormone replacement
- FDA-approved products available for the treatment of cancer
- No information on history of compounding

Recommendation

We **do not recommend** chrysin be included on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act based on consideration of the following criteria: (1) physicochemical characterization; (2) safety; (3) effectiveness; and (4) historical use of the substance in compounding.

Cesium Chloride

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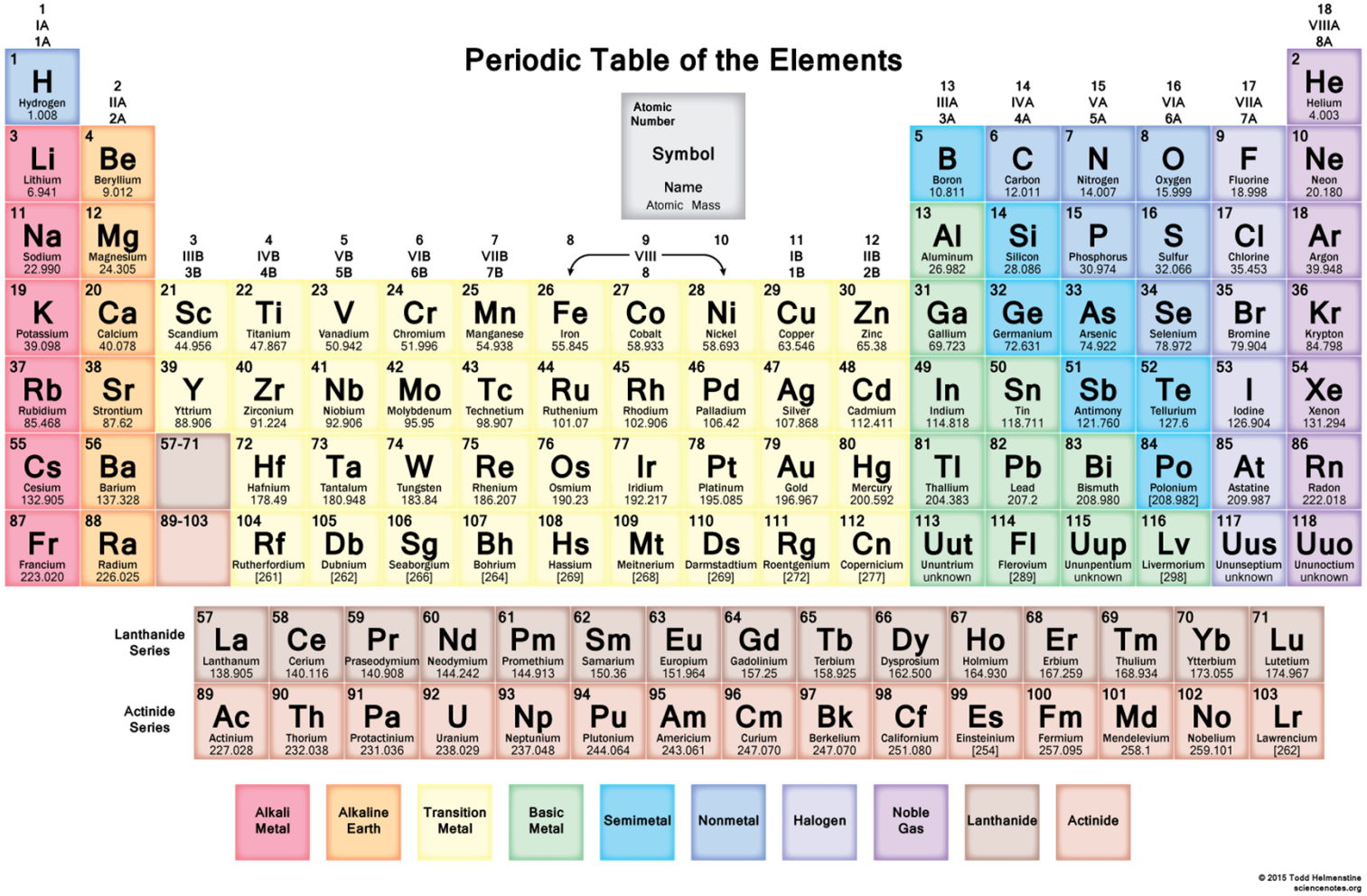
Todd Palmby, PhD, Supervisory Pharmacologist/Toxicologist, DHOT/OHOP

Ramesh Sood, PhD, Senior Scientific Director (Acting), OPQ

Cesium Chloride: Background

- Nomination
  - Use: "For use in combination with other natural substances in treating individuals with numerous types of cancers, by a presumed alkalinizing effect"
  - Route of administration: Slow intravenous infusion
  - References provided in the nomination do not include clinical safety or efficacy data for cesium chloride, although they do include nonclinical information
- Cesium chloride available in the United States as a dietary ingredient in dietary supplements


Periodic Table of the Elements
Atomic Number
Symbol
Name
Atomic Mass
1 IA 1A
2 IIA 2A
3 IIIB 3B
4 IVB 4B
5 VB 5B
6 VIB 6B
7 VIIB 7B
8 VIII 8
9 VIII 8
10 VIII 8
11 IB 1B
12 IIB 2B
13 IIIA 3A
14 IVA 4A
15 VA 5A
16 VIA 6A
17 VIIA 7A
18 VIIIA 8A
1 H Hydrogen 1.008
2 He Helium 4.003
3 Li Lithium 6.941
4 Be Beryllium 9.012
5 B Boron 10.811
6 C Carbon 12.011
7 N Nitrogen 14.007
8 O Oxygen 15.999
9 F Fluorine 18.998
10 Ne Neon 20.180
11 Na Sodium 22.990
12 Mg Magnesium 24.305
13 Al Aluminum 26.982
14 Si Silicon 28.086
15 P Phosphorus 30.974
16 S Sulfur 32.066
17 Cl Chlorine 35.453
18 Ar Argon 39.948
19 K Potassium 39.098
20 Ca Calcium 40.078
21 Sc Scandium 44.956
22 Ti Titanium 47.867
23 V Vanadium 50.942
24 Cr Chromium 51.996
25 Mn Manganese 54.938
26 Fe Iron 55.845
27 Co Cobalt 58.933
28 Ni Nickel 58.693
29 Cu Copper 63.546
30 Zn Zinc 65.38
31 Ga Gallium 69.723
32 Ge Germanium 72.631
33 As Arsenic 74.922
34 Se Selenium 78.972
35 Br Bromine 79.904
36 Kr Krypton 84.798
37 Rb Rubidium 85.468
38 Sr Strontium 87.62
39 Y Yttrium 88.906
40 Zr Zirconium 91.224
41 Nb Niobium 92.906
42 Mo Molybdenum 95.95
43 Tc Technetium 98.907
44 Ru Ruthenium 101.07
45 Rh Rhodium 102.906
46 Pd Palladium 106.42
47 Ag Silver 107.868
48 Cd Cadmium 112.411
49 In Indium 114.818
50 Sn Tin 118.711
51 Sb Antimony 121.760
52 Te Tellurium 127.6
53 I Iodine 126.904
54 Xe Xenon 131.294
55 Cs Cesium 132.905
56 Ba Barium 137.328
57-71
72 Hf Hafnium 178.49
73 Ta Tantalum 180.948
74 W Tungsten 183.84
75 Re Rhenium 186.207
76 Os Osmium 190.23
77 Ir Iridium 192.217
78 Pt Platinum 195.085
79 Au Gold 196.967
80 Hg Mercury 200.592
81 Tl Thallium 204.383
82 Pb Lead 207.2
83 Bi Bismuth 208.980
84 Po Polonium [208.982]
85 At Astatine 209.987
86 Rn Radon 222.018
87 Fr Francium 223.020
88 Ra Radius 226.025
89-103
104 Rf Rutherfordium [261]
105 Db Dubnium [262]
106 Sg Seaborgium [266]
107 Bh Bohrium [264]
108 Hs Hassium [269]
109 Mt Meitnerium [268]
110 Ds Darmstadtium [269]
111 Rg Roentgenium [272]
112 Cn Copernicium [277]
113 Uut Ununtrium unknown
114 Fl Flerovium [289]
115 Uup Ununpentium unknown
116 Lv Livermorium [298]
117 Uus Ununseptium unknown
118 Uuo Ununoctium unknown
Lanthanide Series
57 La Lanthanum 138.905
58 Ce Cerium 140.116
59 Pr Praseodymium 140.908
60 Nd Neodymium 144.242
61 Pm Promethium 144.913
62 Sm Samarium 150.36
63 Eu Europium 151.964
64 Gd Gadolinium 157.25
65 Tb Terbium 158.925
66 Dy Dysprosium 162.500
67 Ho Holmium 164.930
68 Er Erbium 167.259
69 Tm Thulium 168.934
70 Yb Ytterbium 173.055
71 Lu Lutetium 174.967
Actinide Series
89 Ac Actinium 227.028
90 Th Thorium 232.038
91 Pa Protactinium 231.036
92 U Uranium 238.029
93 Np Neptunium 237.048
94 Pu Plutonium 244.064
95 Am Americium 243.061
96 Cm Curium 247.070
97 Bk Berkelium 247.070
98 Cf Californium 251.080
99 Es Einsteinium [254]
100 Fm Fermium 257.095
101 Md Mendelevium 258.1
102 No Nobelium 259.101
103 Lr Lawrencium [262]
Alkali Metal
Alkaline Earth
Transition Metal
Basic Metal
Semimetal
Nonmetal
Halogen
Noble Gas
Lanthanide
Actinide
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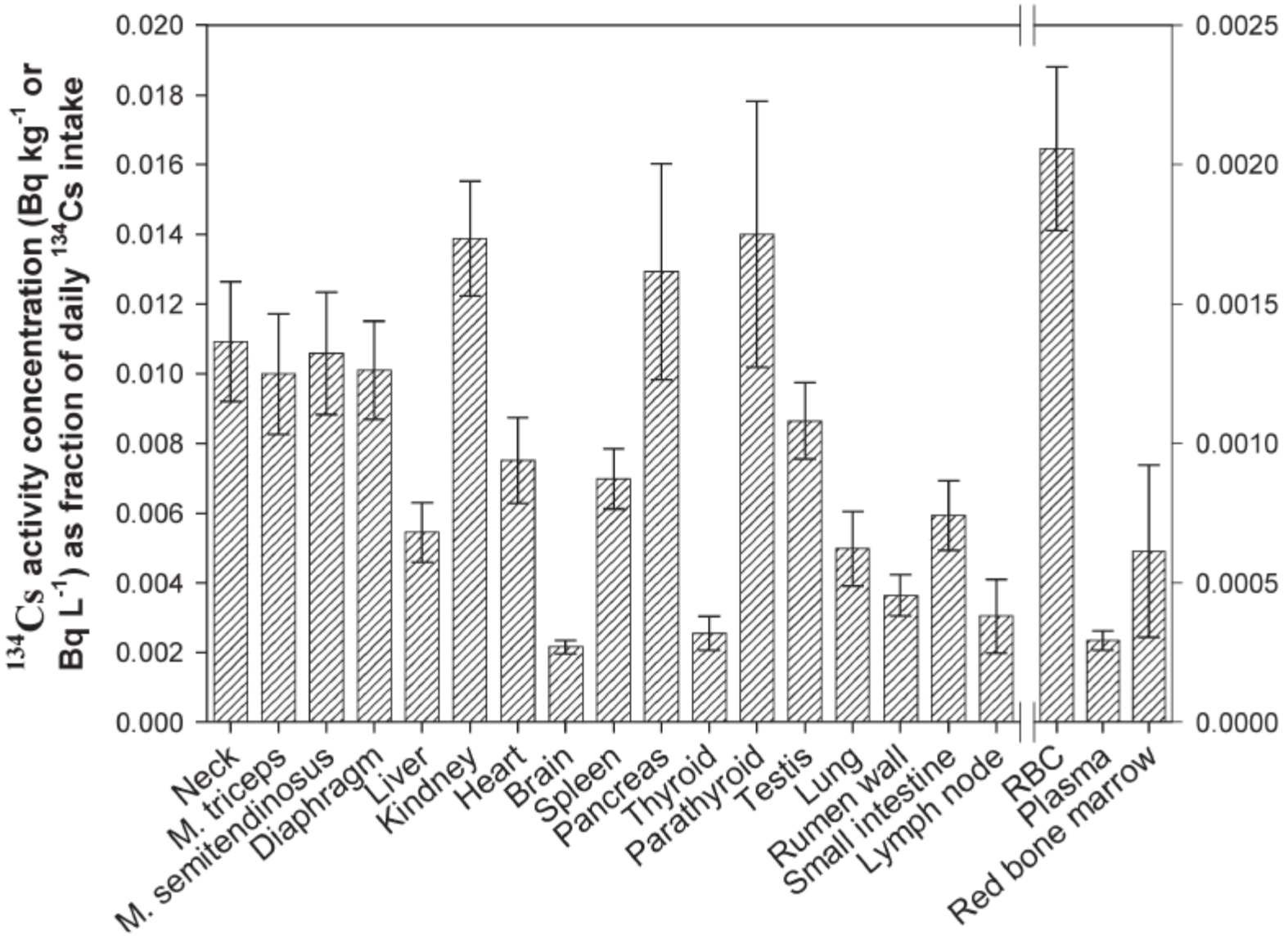
sciencenotes.org

Chemistry Considerations for Cesium Chloride

- Obtained from liquid extraction of concentrated brine (usually seawater)
- Can be easily characterized
- Highly soluble in water
- Stable in aqueous solution



Source: Skuterud, Rad Env Biophys 2004;43:293

Evaluation of Effectiveness

- Suggested mechanism of action as alkalinizing agent

The High pH Therapy for Cancer Tests on Mice and Humans

A. KEITH BREWER

Science Department, A. Keith Brewer Library, Richland Center, WI 53581

BREWER, A K *The high pH therapy for cancer tests on mice and humans* PHARMACOL BIOCHEM BEHAV **21:** Suppl 1, 1–5, 1984 —Mass spectrographic and isotope studies have shown that potassium, rubidium, and especially cesium are most efficiently taken up by cancer cells. This uptake was enhanced by Vitamins A and C as well as salts of zinc and selenium The quantity of cesium taken up was sufficient to raise the cell to the 8 pH range. Where cell mitosis ceases and the life of the cell is short Tests on mice fed cesium and rubidium showed marked shrinkage in the tumor masses within 2 weeks. In addition, the mice showed none of the side effects of cancer Tests have been carried out on over 30 humans In each case the tumor masses disappeared Also all pains and effects associated with cancer disappeared within 12 to 36 hr; the more chemotherapy and morphine the patient had taken, the longer the withdrawal period Studies of the food intake in areas where the incidences of cancer are very low showed that it met the requirements for the high pH therapy

Evaluation of Effectiveness

- Single case series in published literature
- Insufficient information to establish effectiveness of cesium
- FDA-approved products available for treatment of cancer

Cesium Therapy in Cancer Patients

H. E. SARTORI

Life Science Universal Medical Center, Suite 306
4501 Connecticut Avenue, Washington, DC 20008

SARTORI, H E *Cesium therapy in cancer patients* PHARMACOL BIOCHEM BEHAV **21:** Suppl 1, 11–13, 1984 —The effect of cesium therapy on various cancers is reported A total of 50 patients were treated over a 3 year period with CsCl The majority of the patients have been unresponsive to previous maximal modalities of cancer treatment and were considered terminal cases The Cs-treatment consisted of CsCl in addition to some vitamins, minerals, chelating agents and salts of selenium, potassium and magnesium In addition, a special diet was also instituted There was an impressive 50% recovery of various cancers, i e , cancer of unknown primary, breast, colon, prostate, pancrease, lung, liver, lymphoma, ewing sarcoma of the pelvis and adeno-cancer of the gallbladder, by the Cs-therapy employed There was a 26% and 24% death within the initial 2 weeks and 12 months of treatment, respectively A consistant finding in these patients was the disappearance of pain within the initial 3 days of Cs-treatment The small number of autopsies made showed the absence of cancer cells in most cases and the clinical impression indicates a remarkably successful outcome of treatment

Evaluation of Safety

- Nonclinical studies
  - Identified CNS and cardiovascular toxicity
  - Genetic toxicology studies suggest possible chromosomal aberration effects; no carcinogenicity data
  - Reproductive studies show decreased body and organ weight
- Clinical studies and adverse event reporting to FDA: cardiac toxicity

Clinical Toxicology (2009) **47**, 592–594

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650902997831

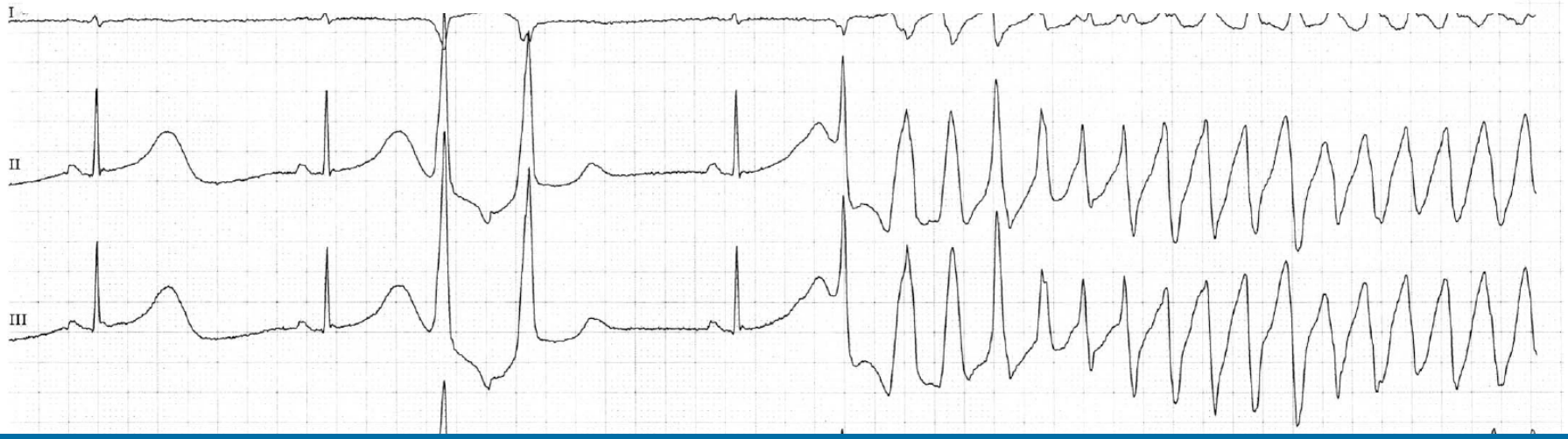
inform
healthcare

BRIEF COMMUNICATION

Life-threatening *Torsades de Pointes* resulting from "natural" cancer treatment

C.K. CHAN[1], M.H.M. CHAN[2], M.L. TSE[1], I.H.S. CHAN[2], R.C.K. CHEUNG[2], C.W.K. LAM[2], and F.L. LAU[1]

[1]*Hong Kong Poison Information Centre, United Christian Hospital, Kwun Tong, Hong Kong, China*
[2]*Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China*



Historical Use in Compounding

- Published literature indicates that cesium chloride used in the treatment of cancer since at least the 1980s
- Currently, oral cesium chloride advertised by a number of compounding pharmacies

Summary

- Cesium chloride is easily characterized and stable in aqueous solution
- Cesium chloride not shown to be effective for the treatment of any cancer
- Fatal ventricular arrhythmias reported as a result of cesium chloride administration
- Other FDA-approved agents with established records of safety and efficacy for some cancers
- Historical information on compounding of IV formulation not found

Recommendation

We **do not recommend** cesium chloride be included on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act based on the following criteria: (1) physicochemical characterization; (2) safety; (3) effectiveness; and (4) historical use of the substance in compounding.

Sodium Dichloroacetate

Pharmacy Compounding Advisory Committee Meeting

June 23, 2016

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Ramesh Sood, PhD, Senior Scientific Director (Acting), OPQ

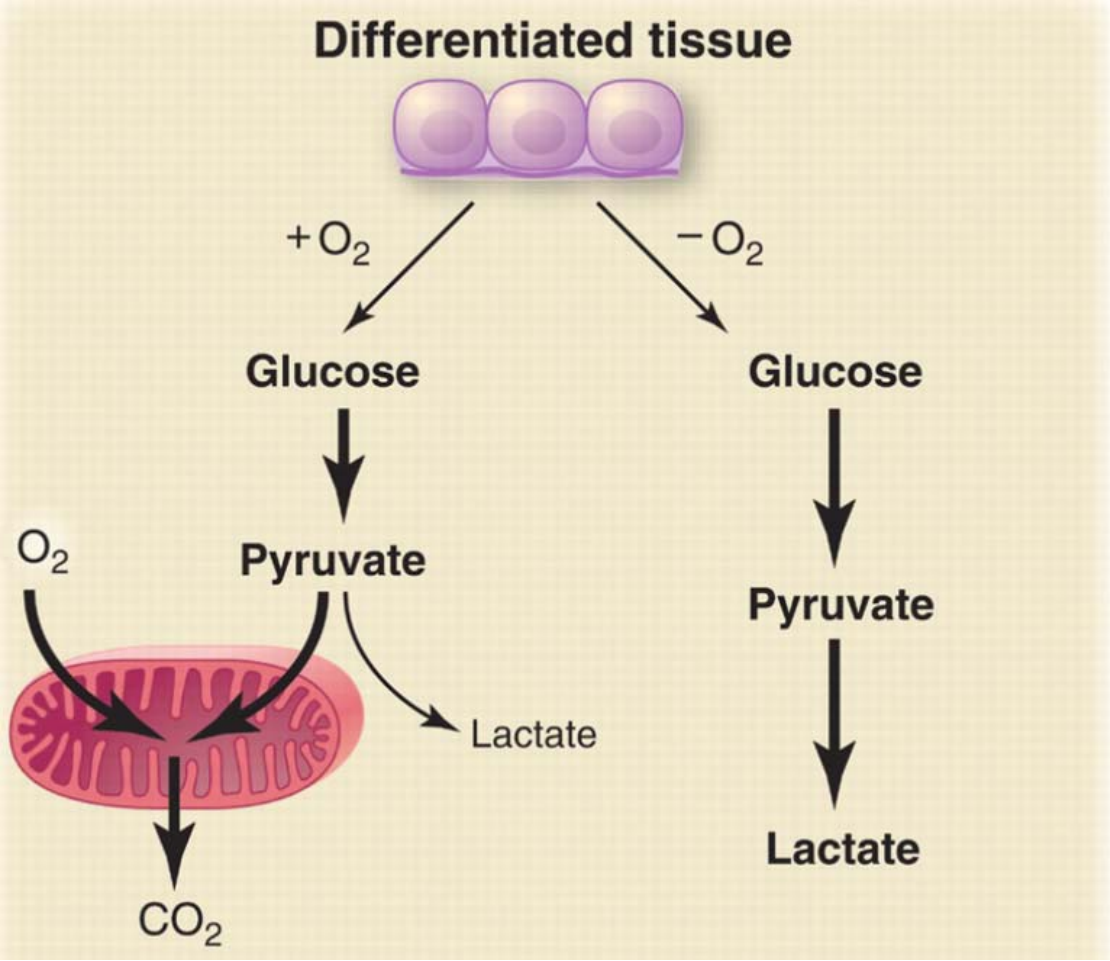
Sodium Dichloroacetate: Background

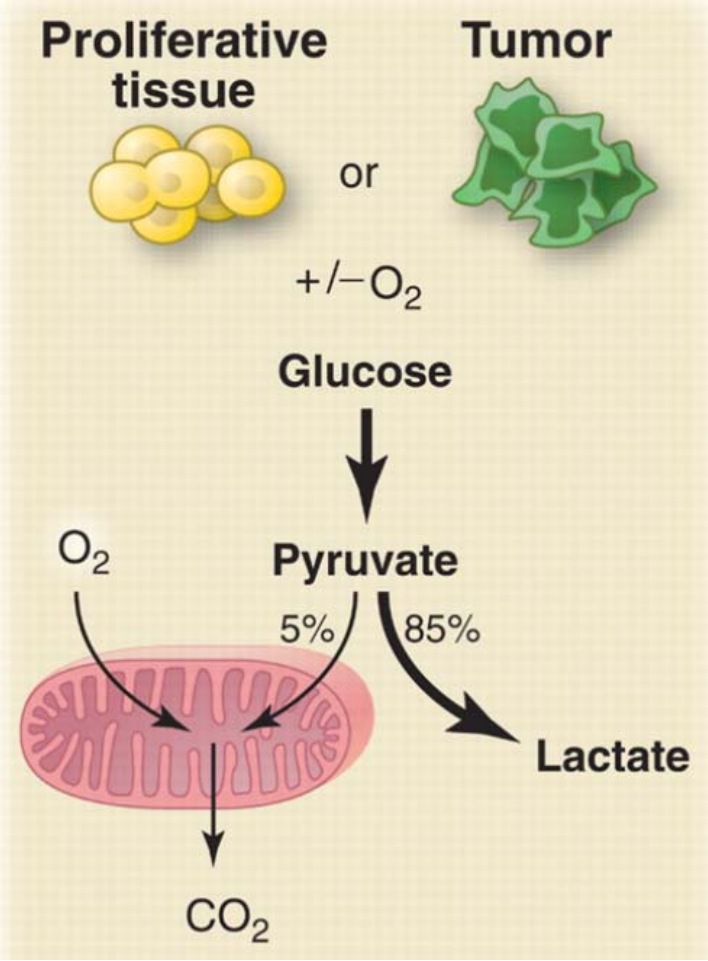
- Nomination
  - Use: "Adjunct treatment for cancer"
  - Route of administration: Oral and intravenous injection
  - References provided in the nomination do not include clinical safety and efficacy data for dichloroacetate, although they do include nonclinical information
- Dicholoroacetate is available as a dietary ingredient in dietary supplements

Chemistry Considerations for Dichloroacetate

- Small molecule synthesized from acetic acid
- Can be easily characterized
- Stable in oral dosage form at low temperatures
- Unlikely to be stable as injectable solution

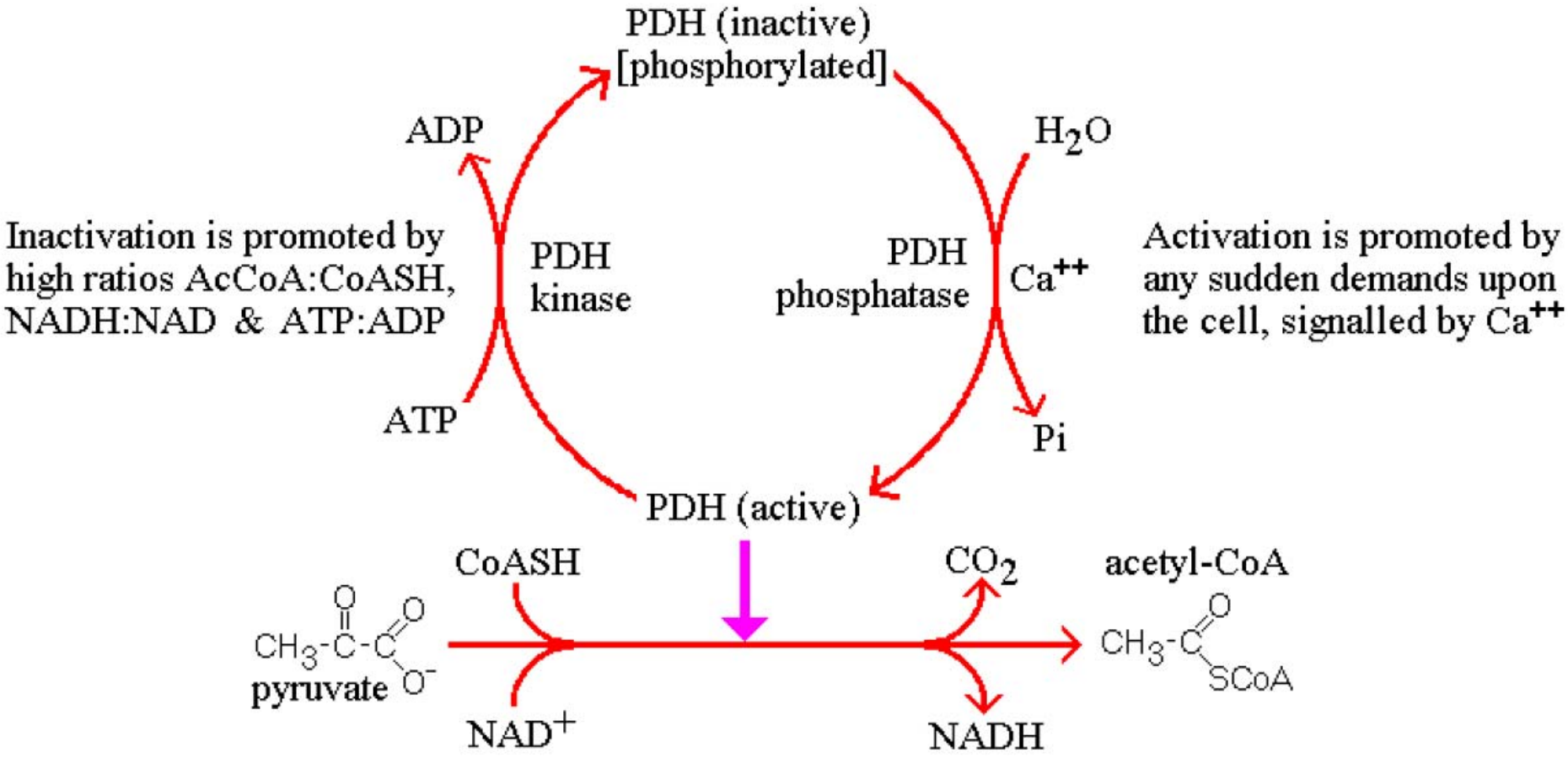
The Warburg Effect



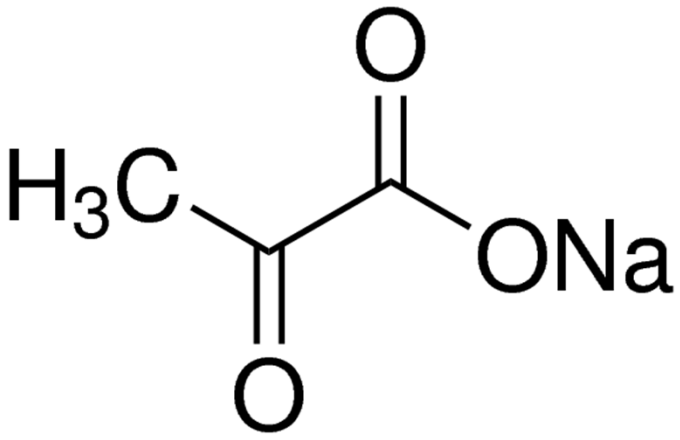


Source: www.cancersavelife.blogspot.com

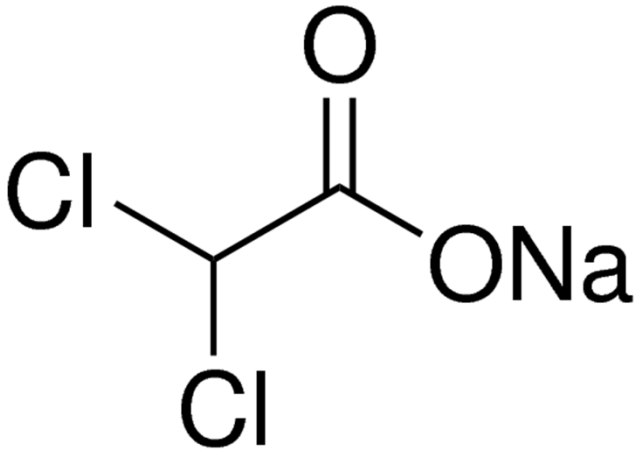
Regulation of Pyruvate Metabolism



Source: www.bmb.leeds.ac.uk



Pyruvate



Dichloroacetate

Pharmacokinetics of Dichloroacetate

- Bioavailability in healthy volunteers 27 to 100%
- Dehalogenated by hepatic glutathione transferase zeta (GSTz1)/maleylacetoacetate isomerase (MAAI) to monochloroacetate and glyoxylate. Of four human polymorphisms of GSTz1, one has 10-fold higher binding affinity for DCA than others.
- After single infusions in healthy volunteers, C_{max} dose proportional up to 30 mg/kg, after which clearance decreased, likely due to inhibition of GSTz1 by DCA.
- Plasma clearance ↓ in patients with cirrhosis

Evaluation of Safety: Environmental Dichloroacetate

- Present in chlorinated water
- EPA-established carcinogen

Evaluation of Safety: Published Clinical Trials

Author	Pop.	Treatment	Results
Kaufmann	MELAS (n = 30)	25 mg /kg PO BID	• Poorly tolerated due to neuropathy
Chu	Advanced solid tumors (n = 24)	6.25-12.5 mg BID	• Toxicities: fatigue, nausea, vomiting, diarrhea, neuropathy • RP2D: 6.25 mg BID
Dunbar	Recurrent brain tumors (n = 15)	Based on GSTZ1/MAAI haplotype	• Toxicity: neuropathy • DLT: none

Kaufmann, Neurology 2006;66:324
Chu, Invest New Drugs 2015;33:603
Dunbar, Invest New Drugs 2014;32:452

Evaluation of Effectiveness

- No clinical trials have been identified that demonstrate a benefit of dichloroacetate in the treatment of cancer
- FDA approved products available for treatment of cancer

Historical Use in Compounding

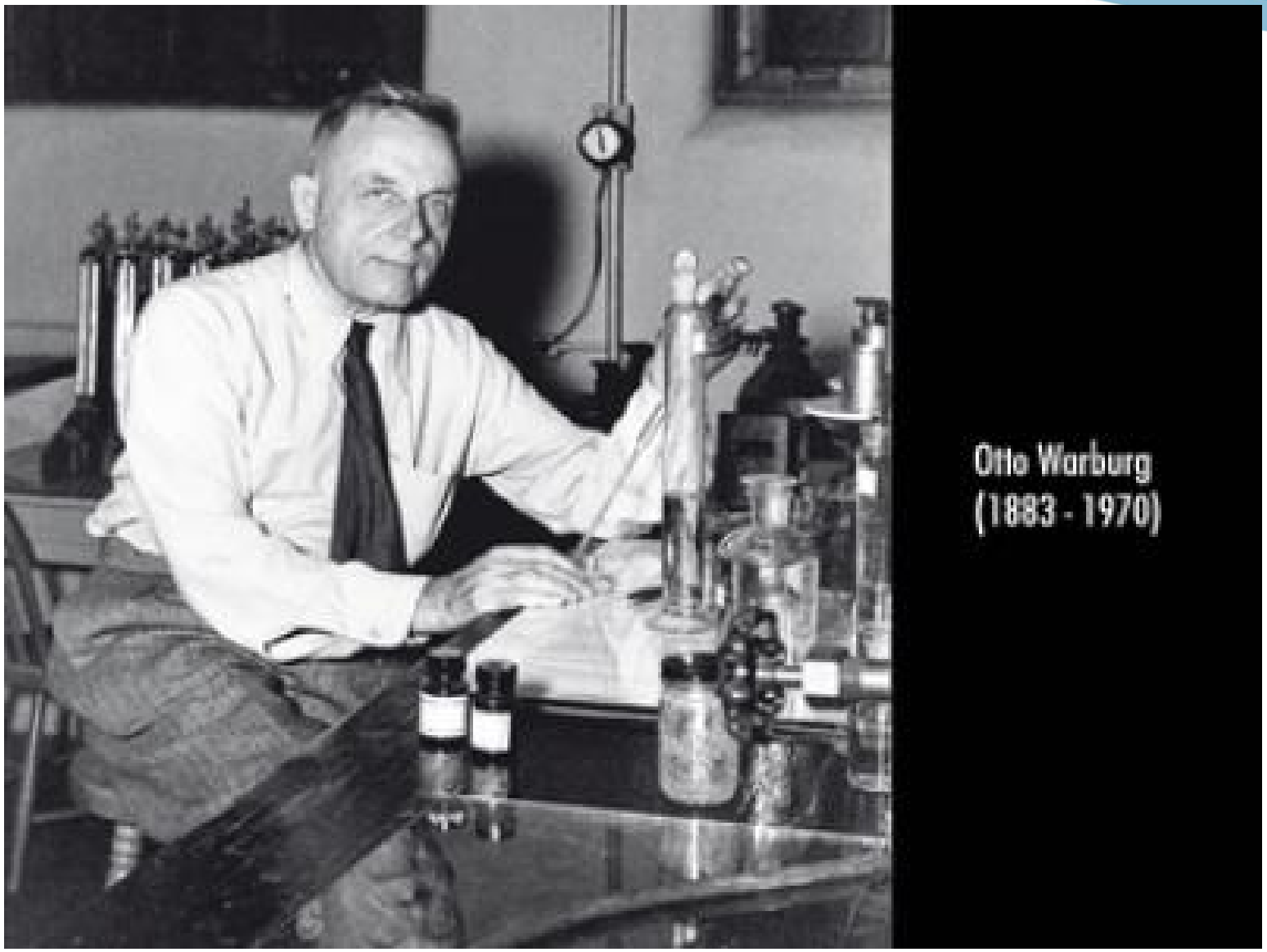
- Insufficient information to determine how long dichloroacetate has been used in compounding

Summary

- Can be easily characterized, is stable in oral dosage form at low temperatures, but is unstable as injectable dosage form
- Safety concerns
  - Significant inter-individual variation in absorption and excretion; drug accumulation over time
  - Peripheral neuropathy, gastrointestinal symptoms, death
  - Secondary malignancies resulting from ineffective treatment
- No demonstrated benefit in cancer treatment, alone or as an adjunct with other therapy
- Insufficient information to assess historical use in compounding

Recommendation

We **do not recommend** sodium dichloroacetate be included on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act based on consideration of the following criteria: (1) physicochemical characterization; (2) safety; (3) effectiveness; and (4) historical use of the substance in compounding.



Source: www.healthywaterlife.com

Expanded Access IND Basics

Pharmacy Compounding Advisory Committee
June 23, 2016

Jonathan P Jarow, MD
Senior Medical Advisor
Office of the Center Director
CDER

Questions

- Is there a model for expanded access to an unapproved drug?
  - Yes
- Can the sponsor charge patients?
  - Yes
- Can administrative costs be passed on?
  - Yes
- Who can be the sponsor?
  - Manufacturer, individual physicians, etc.
- How is the drug dispensed?
  - Sponsor dispenses the drug directly or through an investigator
- Are multiple courses of treatment possible?
  - Yes, provided applicable requirements are met

Eligibility Criteria

- Serious or immediately life-threatening condition
- No comparable or satisfactory alternative therapy
- Potential patient benefit justifies the potential risks, and the risks are not unreasonable in the context of the disease or condition to be treated
- Providing drug will not interfere with clinical investigations that could support marketing approval of the expanded access use

(21 CFR 312.305)

Types of Expanded Access

- Access to an investigational drug outside of a clinical trial setting
- Submitted as an IND or a protocol under an existing IND
- **Single patient** (including for emergency use)
- **Intermediate – size patient populations**
- **Treatment** (widespread use)

21 CFR part 312

Intermediate-sized Access IND

- Application must state whether the drug is being developed for marketing
- Many healthcare providers treating patients with investigational drug under a single IND sharing:
  - IRB
  - Protocol
  - Consent form

21 CFR 312.315

Key Components of an IND

- Identify a sponsor and principal investigator
- Write a protocol and informed consent
- Create an investigator brochure*
- Identify a manufacturer

*ICH E6

Need Help Getting Started?

- Contact the review Division in Office of New Drugs
  - Indication specific
- Contact Division of Drug information (DDI) in CDER
  - (855) 543-3784, or
  - (301) 796-3400
  - druginfo@fda.hhs.gov
- Office of Health and Constituent Affairs
  - (301) 796-8460
- Recommend copying CDER Compounding Team at Compounding@fda.hhs.gov

Pre-IND Meeting

- Strongly recommended as it can be very helpful
- What you should submit in advance of the meeting
  - Background information on plan
  - Specific Questions may be about:
    - Chemistry and manufacturing controls
    - Safety documentation: toxicology or clinical
    - Protocol
- Venue
  - Face-to-face
  - Telephone
  - Written responses

IND Submission (1)

- Investigator Qualifications (CV)
  - Includes subinvestigators
- Drug product information (all manufacturing sites)
  - Purity, strength, and quality
  - Stability
  - Distribution
- Safety
  - Evidence that the drug is safe at the dose and duration proposed
  - Nonclinical/clinical
- Efficacy
  - Rationale for the intended use of the drug
  - At least preliminary clinical evidence of effectiveness (or of a plausible pharmacological effect)

IND Submission (2)

- Protocol
  - Description of disease or condition
  - Proposed method of administration, dose, and duration
  - Eligibility criteria
  - Clinical procedures and monitoring to evaluate effects and minimize risk
- Informed consent form and IRB approval
- Statement about product development
- Investigator brochure

Regulatory Responsibilities

- Cannot begin treatment for 30 days unless you receive notification from FDA (and IRB approval)
- Submission of IND safety reports and annual reports
- Notification of FDA of any new subinvestigators
- Notification of FDA of any product, manufacturing, or distribution changes
- Annual renewal of charging authorization if charging is requested and authorized

Charging for Investigational Products in Intermediate-size Expanded Access

- Requirements (21 CFR 312.8)
  - Provide reasonable assurance to FDA that charging will not interfere with drug development;
  - Provide documentation of calculated amount; and
  - Provide a statement that an independent certified public accountant reviewed and approved the calculation
- Can recover direct drug costs
- Can recover costs of monitoring, IND reporting requirements, and other administrative costs directly associated with the expanded access use
- Can recover fees paid to third party administrator

Resources

- Expanded Access Web site (General)
  - http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm
- CGMP for Phase 1 Guidance
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.pdf
- Charging for Investigational Drugs
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351264
- IND meetings
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM437431

Resources

- Form 1571 – IND application general information
  - http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM182850.pdf
- Form 1572 – IND investigator information
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf
- 21 CFR part 312
- ICH E6 Good Clinical Practices
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Pyruvic Acid

Pharmacy Compounding Advisory Committee Meeting

June 23, 2016

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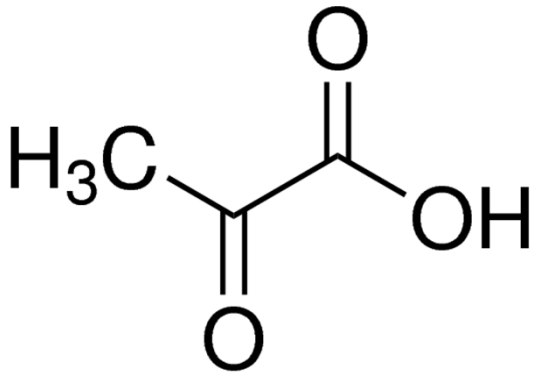
Pyruvic Acid

- Pyruvic acid (40-50%) has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use in the treatment of acne, melasma, and warts.

Physical and Chemical Characterization - 1

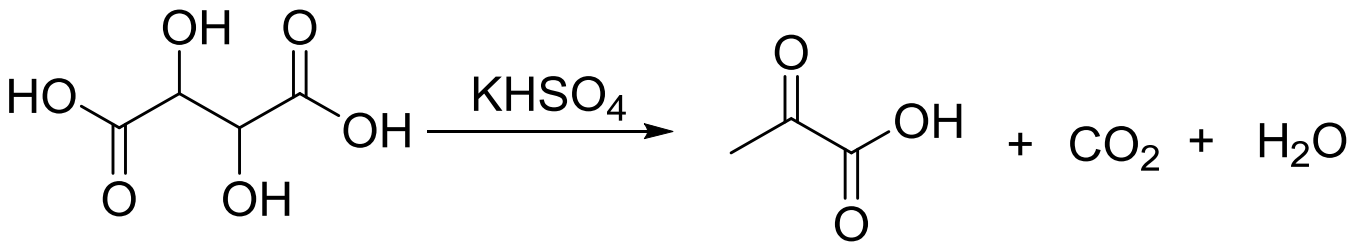
- **Formula:** $C_3H_4O_3$
- **Molecular Weight:** 88.06 g/mol
- **Melting Point:** 11.8 °C (dec.)
- **Solubility:** Soluble in water



- **Stability:** Pyruvic acid can undergo decarboxylation reactions under basic and neutral conditions, and it is also sensitive to sunlight. It is unlikely to be stable in ambient environments.
- **Structure Characterization:** Well characterized

Physical and Chemical Characterization - 2

- **One possible synthetic route:**



- **Likely Impurities:** Trace amounts of starting material and byproducts (acetic acid and lactic acid).
- **Conclusion:** Pyruvic acid is a well-characterized small molecule. In the proposed dosage form it is unlikely to be stable without proper storage (carefully sealed, isolated from moisture, kept away from light).

Pyruvic Acid – Nonclinical Assessment - 1

- Pharmacology
  - Pyruvic acid is an intermediate compound created in the metabolism of carbohydrates, proteins and fats.
  - Its main metabolite is pyruvate, a product of glycolysis.
- Repeat Dose Toxicity
  - Very few repeat dose studies have been conducted with pyruvic acid. Acute studies show that pyruvic acid causes skin irritation and/or corrosion, as well as eye damage.
  - There is a lack of nonclinical data to evaluate the chronic dermal toxicity of pyruvic acid.

Pyruvic Acid – Nonclinical Assessment - 2

- Mutagenicity
  - No information available.

- Developmental and Reproductive Toxicity
  - One study found that pyruvate is metabolized during organogenesis and that interruption of this process could lead to neural tube defects and other developmental toxicities.
  - There is a lack of nonclinical data to evaluate the developmental and reproductive toxicity of pyruvic acid.

Pyruvic Acid – Nonclinical Assessment - 3

- Carcinogenicity
  - No information available.
  - There is a lack of nonclinical data to evaluate the dermal carcinogenicity potential of pyruvic acid.

Human Safety Information - 1

- Reports of "irritation," "erythema," "stinging," "burning."
  - Erythema may persist from minutes to hours.
  - Stinging/burning relieved by neutralization with sodium bicarbonate solution.
- Pain
  - "Discomfort" may signal the desired destructive treatment effect for common warts.
- Reports of "scarring," "pigmentation," "crust."

Human Safety Information - 2

- Pungent vapors that are irritating to the upper respiratory mucosa.
  - Possible risk to patients, providers, and assisting staff in the absence of adequate ventilation.
  - No reports of serious outcomes or undue safety concerns.
- No pharmacokinetic information.
- No information on long-term outcomes.
  - Scarring reported as a risk.

Clinical Efficacy - 1
Tosson et al., (2006)

- Evaluated pyruvic acid in 60 subjects: papulopustular acne (30 subjects), melasma (15), and common warts (15).
  - Acne and melasma treated with 40-50% pyruvic acid peel every 2 weeks for 1-3 months.
  - Warts treated with 70% pyruvic acid paint twice daily for 2-3 weeks.

Clinical Efficacy - 2
Tosson et al., (2006)

Results reported:

- Acne: complete disappearance of acne lesions in 10 subjects (33.3%); disappearance of > 75% of lesions in 6 (20%).
- Melasma: improvement > 50% in 3 subjects (20%); improvement > 25-50% in 5 (33.3%).
- Warts: total clearing of all warts in 12 subjects (80%) and improvement (not otherwise specified) in 3 (20%).

Clinical Efficacy- 3: Acne
Cotellessa et al., (2004)

- Conducted an open-label study of 40 subjects with papulopustular acne.
  - Treatment: 40–50% pyruvic acid every 2 weeks for 3-4 months.
  - Results: clinical disappearance of lesions in 16 subjects (40%); improvement of lesions, without complete disappearance in 20 subjects (50%); and no improvement in 4 subjects (10%).

Clinical Efficacy - 4: Melasma
Ardigo et al., (2010)

- Pilot study using reflectance confocal microscopy to evaluate pigment distribution in melasma in 15 subjects; evaluated treatment response in 7 of these subjects.
  - Subjects received "six cycles of skin peeling with 50% pyruvic acid every day for 2 weeks, followed by topical application of a Kligman's formula containing 2% hydroquinone, applied daily for a total of 5 months of treatment."
  - Treatment outcomes included "a major reduction in pigmented keratinocytes in the epidermis" in 2 subjects, with 3 others showing trace pigment by microscopy.

Clinical Efficacy - 5: Melasma Berardesca et al., (2006)

- Evaluated a 50% pyruvic acid formulation in 20 subjects affected by photodamage, superficial scarring, or melasma.
  - The authors did not state how many subjects were affected by each condition.
  - Performed 4 peeling sessions (3 to 5 minutes) once every 2 weeks. Neutralized with a 10% sodium bicarbonate in water solution.
  - Treatment outcomes included "a significant reduction in the degree of pigmentation in patients with melasma."

Clinical Efficacy - 6: Warts
Halasz (1998)

- Reviewed the charts of 56 patients who had common warts treated with plain 70% pyruvic acid (PA; 18 patients) or a combination formulation of 70% pyruvic acid with 0.5% 5-fluorouracil (PA-5FU; 38 patients).

  - ~75% of patients used the prescribed product for 1 to 4 weeks, and 25% used the product for 1 to 2 months.

Clinical Efficacy - 7: Warts
Halasz (1998)

Results by Pyruvic Acid Formulation (Halasz's Table 3)

Formulation	**Cleared (%)**	**Improved (%)**	**No Change (%)**	**Total**
PA-5FU	22 (58)	10 (26)	6 (16)	38
PA	14 (78)	0 (0)	4 (22)	18
Total	36 (64)	10 (18)	10 (18)	56

Cleared=all warts resolved
Improved=some, but not all, treated warts resolved or warts decreased appreciably in size.
No change=minimal or no decrease in size.

Clinical Efficacy - 8: Warts
Shahmoradi et al., (2015)

- Conducted a randomized, controlled trial in 60 subjects with multiple (≥ 2) plantar warts.
  - Subjects received 70% pyruvic acid or a 16.7% salicylic acid solution twice daily for 4 weeks.
  - Results: number and size of warts were decreased in both groups.
  - The authors found no difference in efficacy between the products.

Approved Alternatives - 1
Acne

- *Antibiotics*:

  Topical: clindamycin phosphate, erythromycin, sodium sulfacetamide.

  Systemic: minocycline.
- *Bacteriostatics*: benzoyl peroxide.
- *Topical Retinoids*: adapalene, tretinoin, tazarotene.
- *Combination Products*: clindamycin/tretinoin, adapalene/benzoyl peroxide.
- *Hormonal*: drospirenone/ethinyl estradiol (hormonal therapy is indicated only if the patient desires an oral contraceptive for birth control).
- *Other*: azelaic acid.

Approved Alternatives - 2
Melasma and Warts

- **Melasma:** fluocinolone acetonide (0.01%)/hydroquinone (4.0%)/ tretinoin (0.05%) Cream.
  - Indicated for the short-term treatment of moderate-to-severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.
- **Warts:** approved prescription therapies available only for genital warts; OTC therapies available for non-genital warts.

Historical Use in Compounding

- Pyruvic acid has been used in pharmacy compounding for at least 30 years.
- Other dermatologic conditions that pyruvic acid has been used to treat include seborrheic keratosis, actinic keratosis, and photoaging.
- The precise extent of use could not be determined, but appears to be worldwide.

Conclusions

- Pyruvic acid is well characterized physically and chemically.
- Reported adverse reactions generally appeared to be local, temporary, non-serious, and readily manageable.
- No information available suggesting undue concerns from respiratory exposure to vapors.
- Although limited, the available information did not raise any major safety concerns associated with use of pyruvic acid.
- The available information indicates that pyruvic acid may have efficacy in the treatment of acne, melasma, and warts.
- Pyruvic acid has been used in pharmacy compounding for at least 30 years and its use appears to be worldwide.

Recommendation

We recommend that pyruvic acid for topical use ***be included*** on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.

Tea Tree Oil

Pharmacy Compounding Advisory Committee Meeting

June 23, 2016

Hon-Sum Ko, MD, FACP
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Tea Tree Oil

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Tea Tree Oil Nomination - 1

- Tea Tree Oil has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act for topical use in the treatment of nail fungus.
- The final compounded topical formulations nominated are at strengths of 5-10%.

Nail Fungus Infection (Onychomycosis)

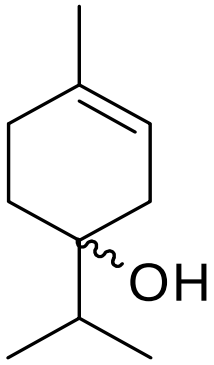
- Most commonly caused by dermatophytes.
- Can also be caused by other fungi, candida species and other yeasts.
- Reported use of Tea Tree Oil for onychomycosis.
  - Applied to nails undiluted.
  - In combination with another antifungal in a diluted formulation, e.g., 5%.

Physical and Chemical Characterization - 1

- Produced by steam distillation of the leaves and terminal branches of a native Australian tree, *Melaleuca alternifolia*.
- Two similar standards established to regulate the quality control of Tea Tree Oil:
  - International Organization for Standardization (ISO 4730; 2004).
  - Standards Association of Australia (AS 2882; 2009).

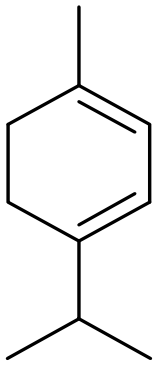
Physical and Chemical Characterization - 2

- A mixture of organic compounds, with >90% of contents being fully characterized monoterpenes, sesquiterpenes, and their associated oxygenated analogs, e.g.



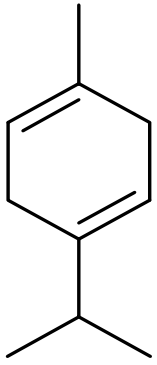
Terpinen-4-ol

≥ 30%



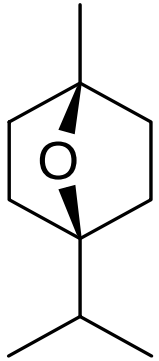
α-terpinene

5-13%



γ-terpinene

10-28%



1,8-cineole

≤ 15%

Physical and Chemical Characterization - 3

- Likely impurities from botanical sources:
  - Heavy metal impurities (e.g., lead, arsenic, mercury) linked to source of starting material for extraction.
  - Bioburden (e.g., microbial content).
- Impurities in Tea Tree Oil expected to be low, because of:
  - Steam distillation not concentrating heavy metals.
  - Tea Tree Oil's antimicrobial activities.

Physical and Chemical Characterization - 4

Conclusions

1. Tea Tree Oil, which meets the ISO/AS standards, is a well-characterized natural product from a native Australian tree, *Melaleuca alternifolia*, produced by a relatively simple extraction process (steam distillation).

Physical and Chemical Characterization - 5

Conclusions

2. The major components in Tea Tree Oil, which meets ISO/AS standards, have been fully characterized and quantified to account for >90% of the contents in a typical sample, and standards are available for control of natural variations.

- Minor components accounting for <10% of Tea Tree Oil content are the same type of terpenoids with similar physical/chemical properties as the major components.
- Complete characterization or quantitative analysis of all components in Tea Tree Oil is not feasible.

Nonclinical Assessment - 1

Pharmacology

- The antifungal properties of Tea Tree Oil have been documented in a number of in vitro and in vivo nonclinical studies.

Acute Toxicity

- Oral LD_{50} for Tea Tree Oil in rats: 1.7 – 2.3 g/kg; rats dosed with 1.5 g/kg Tea Tree Oil appeared lethargic and ataxic and showed depressed activity levels.
- Dermal application of 5 g/kg Tea Tree Oil resulted in two deaths in 10 treated rabbits; dermal application of 2 g/kg Tea Tree Oil caused slight diarrhea in rabbits.

Repeat Dose Toxicity

- No data available.

Nonclinical Assessment - 2

Mutagenicity

- Tea Tree Oil and many of its components were negative in the Ames test. One component, terpineol, exhibited mutagenicity in the Ames test. [Note: Tea Tree Oil has antibacterial/antifungal properties.]
- Tea Tree Oil was not genotoxic in the in vitro human lymphocyte micronucleus and the chromosome aberration tests.
- The components of Tea Tree Oil, including: cineole, D-(+)-limonene, linalool, ι-phellandrene, β-pinene, and β-myrcene, were not genotoxic in in vitro genotoxicity tests conducted with mammalian cells. β-myrcene was not genotoxic in bone marrow cells of rats after oral administration.

- Overall, the available data on the mutagenicity of Tea Tree Oil and its individual components indicate low mutagenic potential.

Nonclinical Assessment - 3

Developmental and Reproductive Toxicity

- No published studies conducted with Tea Tree Oil are available.

- α-Terpinene, ~9% in Tea Tree Oil, induced delayed ossification and skeletal malformations in an oral embryofetal and developmental (EFD) study in rats.

- β-Myrcene, ~0.5% in Tea Tree Oil, caused a higher resorption rate and a higher incidence of retardation and fetal skeleton anomalies in oral EFD studies in rats.

Nonclinical Assessment - 4

Developmental and Reproductive Toxicity (Continued)

- The limited data from the oral rat embryofetal development studies conducted with 2 components of Tea Tree Oil suggest that Tea Tree Oil may pose embryofetal toxicity when ingested orally at relatively high doses; however, the limited data are not adequate to make a final determination.

Nonclinical Assessment - 5

Carcinogenicity

- No published carcinogenicity studies conducted with Tea Tree Oil are available.

- α-Terpineol, 1.5 - 8% in Tea Tree Oil, was not carcinogenic when administered intraperitoneally in a 8-week A/He mouse study; however, this is not a traditional carcinogenicity study design.

- In 2-year oral (gavage) carcinogenicity studies in mice and rats, β-myrcene demonstrated carcinogenic activity in the kidney in rats and the liver in mice.

Nonclinical Assessment - 6

Conclusions

1. Acute toxicity: Tea Tree Oil can be toxic when ingested or topically administered at a high dose.
2. Mutagenicity: Low mutagenic potential.
3. Carcinogenicity, developmental and reproductive toxicity: No data available for Tea Tree Oil, but limited data available for some components suggest risks for embryofetal toxicity or carcinogenicity if administered orally at relatively high doses.
4. Overall, the limited nonclinical safety data available for Tea Tree Oil are not adequate to determine whether neat Tea Tree Oil is safe to use as a bulk drug substance in compounding.

Human Pharmacokinetics

- There are no reports of human pharmacokinetic studies documenting systemic exposure upon application of Tea Tree Oil or its components.
- Overall, data from skin penetration studies suggest that components of Tea Tree Oil can be absorbed following topical application. Under a dosing condition of 10 mg/cm^2, up to 8% of the applied dose penetrated through the epidermis in vitro.

Human Safety - 1

- **Adverse Reactions**
  - Dermal Exposure: irritant and allergic contact dermatitis reactions.
  - Oral Ingestion: central nervous system depression, unsteady gait, abdominal pain, diarrhea, and generalized erythema.
  - Special Concerns: prepubertal gynecomastia, linear IgA disease, and stomatitis/cheilitis.

Human Safety - 2

- **Clinical Trials**
  - Human Dermal Safety Studies:
    - Both neat and diluted (e.g., 5%) Tea Tree Oil can cause skin irritation.
    - Contact sensitization potential ~2% in a study of 150 subjects.
    - There is no information in the literature on human studies to address phototoxicity and photo-allergenicity with Tea Tree Oil.

Human Safety - 3

- **Clinical Trials**
  - We have not found safety data from clinical trials using Tea Tree Oil in compounded product(s).
  - Adverse reactions from clinical trials with Tea Tree Oil are based on use of neat Tea Tree Oil or diluted formulations (e.g., 5%):
    - These include local reactions (irritation, erythema, edema, dryness, itching and scaling).
    - Systemic hypersensitivity has also been reported.

Human Safety - 4

Conclusions

Safety data from use of Tea Tree Oil suggest that:

1. Systemic administration (e.g., oral ingestion) may be associated with significant toxicities.
2. Adverse effects from topical administration are primarily related to irritant and allergic contact dermatitis reactions, although systemic hypersensitivity has also been reported.

Efficacy in Treatment of Onychomycosis - 1

- Two randomized, double-blind, controlled clinical trials involving use of Tea Tree Oil for onychomycosis have been conducted:
  - Buck DS, Nidorf DM and Addino JG. 1994. Comparison of two topical preparations for the treatment of onychomycosis: *Melaleuca alternifolia* (tea tree) oil and clotrimazole.
  - Syed TA, Qureshi ZA, Ali SM et al. 1999. Treatment of toenail onychomycosis with 2% butenafine and 5% *Melaleuca alternifolia* (tea tree) oil in cream.

Efficacy in Treatment of Onychomycosis - 2

- Buck et al., 1994: Compared 2% butenafine HCl plus 5% Tea Tree Oil in a cream base with placebo* cream in 60 subjects (40:20) with toenail nail fungus due to dermatophytes treated under occlusion 3x/day for 8 weeks.
  - After 36 weeks, 80% of subjects who used butanefine HCl/Tea Tree Oil cream, but none of those who used the placebo, had overall cure.**
  - This study demonstrates effectiveness of the combination cream containing 5% Tea Tree Oil. ***In the absence of a treatment arm of butenafine hydrochloride alone, the contribution of 5% TTO is unknown.***

* Placebo was matching cream containing Tea Tree Oil.

** Overall cure was defined as resolution of all symptoms with respect to global assessment plus mycological cure and progressive growth of normal nail.

Efficacy in Treatment of Onychomycosis - 3

- Syed et al., 1999. Compared 1% clotrimazole solution vs neat Tea Tree Oil administered topically 2x/day for 6 months in 117 subjects (53 clotrimazole and 64 Tea Tree Oil) having toenail onychomycosis with dermatophytes.
  - After 6 months of therapy, partial or full clinical resolution was reported in 61% of subjects treated with clotrimazole and 60% with Tea Tree Oil.
  - ***In the absence of a placebo treatment arm, this study does not demonstrate effectiveness of neat Tea Tree Oil. The control, clotrimazole 1% solution, is not an approved treatment for onychomycosis and is inappropriate for comparison (unless statistically inferior to Tea Tree Oil).***

Efficacy in Treatment of Onychomycosis - 4

Conclusions

1.Two randomized, double-blind, controlled clinical trials have been conducted to study the treatment effect of Tea Tree Oil, pure or in combination with an antifungal, in onychomycosis.

2.Efficacy of Tea Tree Oil in onychomycosis has not been established because of:

- Contribution of Tea Tree Oil not demonstrated in a combination product.
- Inappropriate comparison between neat Tea Tree Oil and a product not approved for onychomycosis in the absence of placebo control.

Approved Therapies for Onychomycosis

- Oral Drug Products
  - griseofulvin tablets or oral suspension
  - itraconazole capsules
  - terbinafine tablets
- Topical Drug Products
  - ciclopirox solution
  - tavaborole solution
  - efinaconazole solution

Historical Use in Compounding

- Although Tea Tree Oil-containing products have been commercially available at least since 1982 for use as topical formulations for a wide variety of skin, ocular, oral, and vaginal conditions, there is scant information regarding its use in pharmacy compounding.

Conclusions

- Tea Tree Oil meeting ISO or AS standards is considered well characterized in its physical and chemical properties.
- For topical use, Tea Tree Oil may cause local reactions such as irritation, erythema, edema, dryness, itching, and scaling; systemic hypersensitivity has also been reported.
- There is a lack of evidence of efficacy in the treatment of onychomycosis with Tea Tree Oil.
- There is also a lack of information on the past use of Tea Tree Oil in pharmacy compounding.

Recommendation

We **do not recommend** Tea Tree Oil be included on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.

Dimercapto-1-propanesulfonic Acid (DMPS)

Pharmacy Compounding Advisory Committee Meeting

June 23, 2016

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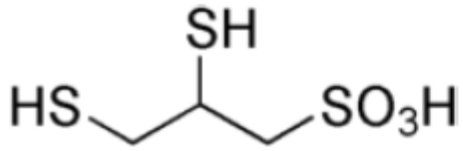
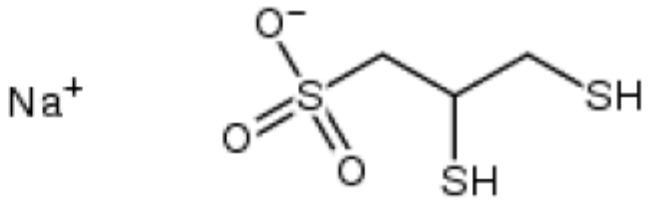
John K. Leighton, PhD, DABT, Division Director, DHOT/OHOP

DMPS: Nomination

- Use: “for treatment of heavy metal poisoning.”
- Route of administration: Oral, Intravenous injection, intramuscular injection.
- Materials received
  - Publications of anecdotal reports and mostly uncontrolled series of cases of exposure to various heavy metals treated with DMPS.

DMPS: Chemistry*





- Most commonly supplied as its sodium salt.
- Non-hygroscopic, exists as monohydrate.
- MW-228.3 Daltons.
- Stable in the crystalline form.
- Relatively stable in aqueous solutions, but labile to oxidation.

* Information based on Heyl Scientific Product Monograph

DMPS: Chemistry (cont) *

- Purified by release from the lead salt.
- Potential in process impurities: lead, allyl bromide, allyl sulfonic acid, and 2,3-dibromopropane-1-sulfonic acid.
- Potential heavy metal contamination can be monitored using USP compendial methods.

* Information based on Heyl Scientific Product Monograph.

DMPS: Nonclinical*

- Pharmacology
  - Mechanism of action not fully characterized.
  - Increases the urinary elimination of arsenic and interferes with arsenic methylation.
  - Promotes excretion and protects against mercury-induced renal damage by inhibiting mercury accumulation in renal proximal and distal tubular cells.
- Toxicokinetics
  - Oral absorption 30% in rats and 60% in dogs with peak plasma concentrations reached after 30 to 45 minutes.
  - Distribution after IV dose mainly into plasma and kidneys.
  - Elimination renal with a serum half-life of about 20 to 60 minutes.

* Based on April 2009 WHO document and Heyl monograph

DMPS: Nonclinical (cont)*

- Safety pharmacology
  - Relatively low acute toxicity; LD50 for parenteral administration approximately 1 to 2 g/kg.
  - Relatively low chronic toxicity in dogs and rats.
  - No evidence of adverse effects on cardiovascular, gastrointestinal, or renal systems.
  - No data available on central nervous system or respiratory system.
- Not mutagenic in the Ames test.
- No reproductive toxicity or teratogenicity shown in animals.
- Information on carcinogenicity is not available.

* Based on April 2009 WHO document and Heyl monograph.

DMPS Safety: Major Associated Adverse Reactions

- Serious case of Stevens-Johnson reported; one death due to severe diffuse desquamation.
- Dermatologic reactions, nausea and vomiting, hypotension, increases in serum transaminases, transient bronchospasm, fever, leukopenia.
- Reactions typically mild or moderate in severity.

DMPS: Clinical Evaluation of Effectiveness

- Uses in published studies and reports include for high arsenic in drinking water, lead poisoning, mercury poisoning, mercury excess from facial cream, mercury-containing dental amalgams, Wilson's disease, high bismuth.
- Most reports are of uncontrolled use or anecdotal reports.
- Literature search found no adequate scientific studies that demonstrate the effectiveness of DMPS for the reported uses.

FDA Approved Drugs for Treatment of Heavy Metal Poisoning

- Multiple available approved drugs for treatment of heavy metal poisoning
  - Calcium disodium versenate (edetate disodium calcium) – lead.
  - Chemet (2,3,-dimercaptosuccinic acid; succimer; DMSA) – lead.
  - BAL (British Anti-Lewisite; dimercaprol) – arsenic, gold, mercury.
  - Cuprimine (penicillamine) – Wilson's disease, cystinuria, severe active rheumatoid arthritis.
  - Syprine (trietine dihydrochloride) – Wilson's disease (2^{nd} line).

DMPS: Historical Use in Compounding

- Reported at 1998 PCAC that compounding dates to mid-1980s.
- Clinical use of DMPS mentioned in literature as early as 1958.
- Internet search suggests main "intended uses"
  - Treatment of persons with presumed mercury toxicity due to mercury amalgam dental fillings.
  - Treatment of persons with autistic disorders.

Conclusions

- DMPS is well defined and can be identified consistently, but manufacture may leave residual impurities, including lead which is toxic.
- Clinical investigation of use of the DMPS has been inadequate to establish safety.
- No clear evidence for clinical benefit of DMPS as currently used.
  - FDA-approved medications are available for treating heavy metal poisoning.
- Historical use dating to 1950s.

Recommendation

- We recommend that DMPS ***not be included*** on the list of bulk drug substances that can be used in compounding under section 503A of the Federal, Food, Drug, and Cosmetic Act.